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REGENERON PHARMACEUTICALS, INC
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EXAMINER

SINGH, ANOOP KUMAR

ART UNIT	PAPER NUMBER
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1632

MAIL DATE	DELIVERY MODE
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08/07/2007

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/804,532

Applicant(s)

CROLL-KALISH ET AL.

Examiner

Anoop Singh

Art Unit

1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 09 May 2007.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☐ Claim(s) 14 and 27-32 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 14, 27-32 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____

- 4) ☒ Interview Summary (PTO-413)
Paper No(s)/Mail Date 7/2/07.
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____

DETAILED ACTION

Applicant's amendments to the claims and response filed on May 9, 2007, has been received and entered. Claims 1-13 and 15-26 have been canceled, while claims 14 has been amended. Applicants have also added claims 27-32 generally directed to elected invention.

Election/Restrictions

Applicants' election of claims 14-17 (Group VII) in the reply filed on October 13, 2006 was acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election was treated as an election without traverse (MPEP § 818.03(a)).

It is noted that applicants have added new claims 27-32 that are generally directed to the elected subject matter. Therefore, these claims will be examined to the extent they encompass elected subject matter of transgenic mouse comprising a deletion of the CIRL-3 like gene.

Claims 14, 27-32 are under current examination.

Withdrawn-Specification

The objection to the disclosure is withdrawn in view of amendments to the specification specifically removing the URLs cited in paragraph 69 of the specification.

Withdrawn-Claim Rejections - 35 USC § 112

Claims 15-16, 18, 19, 21-22 and 23 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn in view of cancellation of claims 15-26. .

New-Claim Rejections-Necessitated by amendments - 35 USC § 112

Claims 14, 27-32 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. 37 CFR 1.118(a) states "No amendment shall introduce new matter into the disclosure of an application after the filing date of the application". In the instant case, the recitation of limitations... "pervasive development disorder-not otherwise specified" (PDD-NOS) " (claims 14, 31 and 32) and "diagnostic criteria" (14, 27-32) are considered new matter. The specification does not provide explicit support for "pervasive developmental disorder-not otherwise specified" and "diagnostic criteria". Upon further review of the instant specification, examiner could only find support for "pervasive development disability-not otherwise specified" (see throughout the specification, eg. Page 2, para. 8 line 7). It is also noted that instant specification provides support to pervasive developmental disability-not otherwise specified (PDD-NOS), which may include compulsive or perseverative behavior. The specification does not provide support to pervasive developmental disorder-not otherwise specified (PDD-NOS) as recited in claims, 14, 31 and 32 or "diagnostic criteria" as recited in claims 14, 27-32. It is noted that claims 27-30 directly or indirectly depend on claim 14.

MPEP 2163.06 notes "If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph-written description requirement. *In re Rasmussen*, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981) teaches that "Whenever the issue arises, the fundamental factual inquiry is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the time application was filed... If a claim is amended to include subject matter, limitation or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in that application".

To the extent the claimed methods are not described in the instant disclosure, claims 14, 27-32 are also rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, since the applicants disclosure do not provide support for "pervasive developmental disorder-not otherwise specified" (PDD-NOS) and "diagnostic criteria" in the specification. The specification does not provide adequate guidance on determining what is included or excluded by the claims and therefore an artisan of skill would require undue experimentation to practice or make and/or use the invention.

Claim Rejections- Necessitated by amendments - 35 USC § 101

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claim 14 remains rejected and newly added claims 27-31 and 32 are also rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific, substantial and credible asserted utility or a well-established utility.

Claims 14, 27-32 are directed to a transgenic mouse comprising a deletion of the endogenous Calcium Independent Receptor of Latrotoxin 3-Like (CIRL3-L) gene, wherein said transgenic mouse exhibits at least one diagnostic criteria of a psychiatric disorder that is an anxiety related disorder selected from Asperger's syndrome, autism and pervasive developmental disorder-not otherwise specified "PDD-NOS). Subsequent claims 27-28 limit the phenotype of transgenic mouse of claim 14 to include mouse that exhibits at least one or two diagnostic criteria for Asperger's syndrome respectively. Claims 29-30 limit the phenotype of transgenic mouse of the invention to include mouse that exhibit at least one or two diagnostic criteria for autism. Claims 31 and 32 limit the phenotype of transgenic mouse of claim 14 to include at least one or two diagnostic criteria for PDD-NOS. In the instant case, claimed transgenic mouse is not supported by either a specific and substantial asserted utility or a well-established utility because the specification fails to assert any substantial and credible asserted utility for the claimed transgenic knockout mouse and neither the specification nor art of record disclose any specific phenotype associated with any disease condition or model for the transgenic mouse comprising a deletion of CIRL-3 gene.

The specification discloses that CIRL3-L, which is a new GPCR protein, has a role in the mediation of psychiatric disorders including anxiety disorders and schizophrenia, as well as nervous and compulsive motor activity (see paragraph 7). The specification describes a non-human transgenic animal comprising a modification of an endogenous CIRL3-L gene is generated by targeting the endogenous CIRL3-L gene with a large targeting vector. The invention embraces a knock-out wherein the CIRL3-L gene is altered or deleted such that the function of the endogenous CIRL3-L protein is reduced or ablated while it also embraces transgenic animal that is a knock-in animal modified to comprise an exogenous human CIRL3-L gene. The specification contemplate transgenic animals are useful in identifying agents that diminish anxiety or modulate other activities that are mediated by the human CIRL3-L protein (see paragraph 23). The specification teaches CIRL-3L knockout mouse were socially impaired. It is noted that specification also discloses that the severity of the impairment was dependent upon the background strain of the mice (emphasis added) (see

examples and Figure 1). The knockout animal also showed gait abnormalities (example 3, figure2), impaired nociceptive responding on the hot plate test (see figure 3) and compulsive motor anxiety as evidenced by increased number of grooming bouts (see examples and figure 4). It is further noted that the instant specification contemplates transgenic animals containing a modified CIRL3-L gene are useful as animal models of anxiety-related disorders, obsessive compulsive behavior or related disorders, screening for agents capable of reducing, ameliorating and/or inhibiting psychiatric disorders, motor activity, perseverative or compulsive behaviors, and anxiety (see paragraph 63 of the specification). However, specification fails to disclose any asserted utility for the mouse as a model or for a method of identifying compound that modulated CIRL-3L in the knockout or knock in mouse model that are found to be specific and/or substantial.

At the time of filing of instant application, an artisan would have not found such utilities evident because specification does not provide a correlation between a CIRL-3 like gene and established function, phenotype or disease. The specification discloses no known function of CIRL-3L gene in the normal physiology or a known pathological state. The specification contemplates that experiments show its function in the mediation of anxiety and anxiety-related motor activity, psychiatric disorders, and the modulation of motor activity. Additionally, specification also discloses that CIRL3-L may be involved in the mediation of seizures and related disorders (see paragraph 40). The specification discloses CIRL-3L as a new GPCR homologue and it is generally known that GPCR are often the target for new therapeutics. The fact that it is new GPCR homologue and has structural similarity does not suggest its specific function or functional importance in any disease or disease model system. The specification of the instant application fails to provide any correlation between the disclosed phenotypes and function or role of CIRL-3L gene in any disease or any disorder. Thus, in order to determine the specific utility for the mice, the Artisan of skill would need to perform further research upon the claimed transgenic mice in order to determine the correlation between the knockouts in and the observed phenotypes relating to PDD-NOS, asperger's syndrome and autism. It is noted that specification describes CIRL3-Like is

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localized to many regions of the brain particularly in the thalamus and anterior cingulate cortex suggesting its role psychiatric disorders (see example 2). Ichtchenko et al (J Biol Chem. 1999 Feb 26; 274(9): 5491-8, art of record) indicated that CIRL-3 is expressed predominantly in brain similarly to CIRL-1 (see abstract). However, neither the specification nor the art disclose any known function or relationship to CIRL-3L gene to any disease. The specification also discloses a CIRL-3L knockout mouse are socially impaired suggesting CIRL-3L has a functional role in anxiety related disorder, and therefore instant knockout and knock in animal can be used as model for any anxiety related disorder more specifically PDD, PDD-NOS and OCD. It is noted that applicants conclusion that a transgenic mouse that has social impairment measured by opening field testing and CIRL3-L KO mice showing decreased sensitivity to cutaneous somatosensation suggesting a sensory gating deficits which is a common abnormalities in schizophrenia, the pervasive developmental disorders (especially autism, Asperger's syndrome, and PDD-NOS), and in attention deficit-hyperactivity disorder (ADHD) (see paragraph 73-75). It is emphasized that open field-testing does not correlate directly to all forms of anxiety related disorder. It is noted that heterozygous mouse were never tested. It is generally known in the art that heterozygous disruption of a gene might have a wild type phenotype while mouse with homozygous disruption have an altered phenotype. In addition, any observed phenotype in homozygous disruption may be because of compensatory system that may be activated to mask the resulting phenotype. These compensatory changes may be due to differential expression of another gene, which may be regulated by the downstream product of the deleted gene (Holschneider et al. Int J Devl Neuroscience, 2000, 18: 615-618, page 615). It is noted that as amended claim 14 recite transgenic mouse comprising a deletion of the CIRL-3 like gene exhibit at least one diagnostic criteria of a psychiatric disorder that is a anxiety related disorder selected form Asperger's syndrome, autism and PDD-NOS. The specification has exemplified social interaction test such as open field, light/dark exploration and elevated plus Maze test to assess diagnostic criteria of the recited psychiatric disorder. It is emphasized that applicants do not provide any specific phenotype that could be attributed to the deletion of CIRL-3L in any mouse. Thus,

asserted utility of using the mice as disease model for any specific condition is not substantial or creditable. As set forth in the utility guideline a general statement of any specific utility, such as model for Asperger's syndrome, autism and PDD-NOS would ordinarily be insufficient. Similarly, a statement of utility for plurality of disease model is non-specific, renders the purported utility of the claimed C1RL-3L knockout mouse to be non-specific. The usefulness of the transgenic knockout mice, as models for disease, is not clear, absence of assessment that they reflect a particular diseases state. Thus, in order to determine the specific utility for the mice, the Artisan of skill would need to perform further research upon the claimed mice in order to determine the correlation between the C1RL3- L gene deletion and the observed phenotypes relating to open field, light/dark exploration and elevated plus Maze test to any specific disorder. Prior to instant invention, Rex et al (Pharmacol Biochem Behav. 1996; 54(1):107-11) indicated that genetic factors and breeding conditions substantially contribute to anxiety-motivated behaviors in animal models. These differences in anxiety-related behavior may also be related to biochemical differences. Rex et al also discuss the differences shown in anxiety-related behavior that might explain sometimes-contradictory effects following the treatment with anxiolytic or anxiogenic drugs. It is further noted that in a post filing art Tsuda et al (Behav Brain Res. 2006; 166(1): 19-31) also show the influence of genetic background of the mice on neurobehavioral traits (see abstract). It is noted that Tsuda et al show that acoustic startle responses were increased in DBA/2 mice and decreased in C3H/He mice, but not altered in C57BL/6 or ddY mice. PPI levels were decreased in DBA/2 and C57BL/6 mice, but not in C3H/He or ddY mice. Locomotor activity was elevated only in DBA/2 mice. Similarly, Rodgers et al (Physiol Behav. 2002; 77(2-3):301-10) also discloses that three different inbred strains were less active as compared with the outbred Swiss-Webster strain in two exploration-based tests of anxiety-related behavior. Thus, it is apparent that pre and post filing art suggested strain, gender and breeding specific alteration in neurobehavioral traits. It is clear that the effect seen after deletion of C1RL3-L gene is not specific, substantial or credible specific phenotype particularly unpredictability in achieving neuro behavioral phenotype in transgenic knockout mice. This leaves the Artisan of skill to speculate the

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uses of the mice and methods as claimed. Under the utility guideline set forth above requirement for further research or experimentation renders the claimed invention as lacking in a specific or substantial utility. Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real-world" context of use are considered substantial utilities. The evidence of record has not provided any other utility for the transgenic mice encompassed by the claims that are substantial and specific because the phenotypes in the transgenic CIRL3-L mice are not specific to any one disease or condition, the Artisan, at the time of filing, would not know how to use the mouse or any data resulting from using the mice. To make such a determination, the Artisan of skill would need to further research to mice, to determine if functions associate with CIRL3-L are present in the mice, and then identify disease or condition associated with the disclosed phenotype. The specific utilities cited in the disclosure require further research to establish whether deletion of CIRL-3L can be attributed to a particular function or utility. The invention of claims 14, 27-32 provides no specific and substantial utility, since no function can be attributed to the transgenic mouse of the invention.

Claims 14, 27-32 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and/or substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Response to Arguments

Applicant's arguments filed May 9, 2007 have been fully considered but they are not fully persuasive. Applicants in their argument on page 5, paragraph 3-5 and on page 6 states that amended claim 14 and new claims 27-32 satisfy the utility requirement. The claimed invention has a specific and a substantial utility. Applicants assert that a specific utility is specific to the subject matter claimed, in contrast with a general utility that is applicable to the broad class of the invention. A substantial utility is one that defines a real world use, which does not require carrying out further research to identify or reasonably confirm a real world context. In this regard, applicants argue that the

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claimed transgenic mouse has utility as a mouse model of a psychiatric disorder, for example, a psychiatric disorder selected from Asperger's syndrome, autism, and PDD-NOS. Applicants refer to the specification, for example, at paragraphs [0008], [0014]-[0019], and in the figures, for example, Figs. 1B-D and Figs. 4A-B. Applicants assert that a person of ordinary skill would recognize that the social interaction tests of Fig. 1, and the Open Field, Light/Dark Exploration, and Elevated Plus Maze tests are standard tests in the art employed to assess diagnostic indicators of the psychiatric disorders recited in the claims. Therefore, a person of ordinary skill in the art would readily recognize that the transgenic mouse exhibits one or more diagnostic criteria (as reflected in the assessment tests shown in the figures) of the recited psychiatric disorders.

In response, it is noted that as amended independent claim 14 embrace a transgenic knockout mouse exhibiting at least one diagnostic criterion of a psychiatric disorder. Examiner would agree that instant specification shows open Field, Light/Dark exploration, and elevated plus maze tests (see figure 1 and 4A-B), however, specification fails to establish any link between deletion of CIRL-3 L gene to any one of these phenotype. Examiner has cited ample evidence to indicate that many of the behavioral test and neurobehavioral traits as argued by applicants are also influence by genetic background and breeding conditions of the mice (supra). Furthermore, neither prior art nor instant specification establishes any nexus between CIRL3-L gene and Asperger's syndrome, autism and PDD-NOS. The evidence of record has not provided any other utility for the transgenic mice encompassed by the claims that are substantial and specific because the phenotypes in the transgenic CIRL3-L mice are not specific to any one disease or condition, the artisan, at the time of filing, would not know how to use the mouse or any data resulting from using the mice. To make such a determination, the Artisan of skill would need to further research to mice, to determine if functions associate with CIRL3-L are present in the mice, and then identify disease or condition associated with the disclosed phenotype. The specific utilities cited in the disclosure require further research to establish whether deletion of CIRL-3L can be attributed to a particular function or utility.

Claim Rejections- Necessitated by amendments - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 14 stands rejected and newly added claims 27-32 are also rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In determining whether Applicant's claims are enabled, it must be found that one of skill in the art at the time of invention by applicant would not have had to perform "undue experimentation" to make and/or use the invention claimed. Such a determination is not a simple factual consideration, but is a conclusion reached by weighing at least eight factors as set forth in In re Wands, 858 F.2d at 737, 8 USPQ 1400, 2d at 1404. Such factors are: (1) The breadth of the claims; (2) The nature of the invention; (3) The state of the art; (4) The level of one of ordinary skill in the art; (5) The level of predictability in the art; (6) The amount of direction and guidance provided by Applicant; (7) The existence of working examples; and (8) The quantity of experimentation needed to make and/or use the invention.

The office has analyzed the specification in direct accordance to the factors outlines in *In re Wands*. MPEP 2164.04 states: "[W]hile the analysis and conclusion of a lack of enablement are based on factors discussed in MPEP 2164.01(a) and the evidence as whole, it is not necessary to discuss each factor in written enablement rejection." These factors will be analyzed, in turn, to demonstrate that one of ordinary skill in the art would have had to perform "undue experimentation" to make and/or use the invention and therefore, applicant's claims are not enabled.

Claim 14 has been amended to recite a transgenic mouse comprising a deletion of the endogenous Calcium Independent Receptor of Latrotoxin 3-Like (CIRL3-L) gene, wherein said transgenic mouse exhibits at least one diagnostic criteria of a psychiatric disorder that is an anxiety related disorder selected from Asperger's syndrome, autism and pervasive developmental disorder-not otherwise specified "PDD-NOS). Subsequent claims 27-28 limit the phenotype of transgenic mouse of claim 14 to include mouse that exhibits at least one or two diagnostic criteria for Asperger's syndrome respectively. Claims 29-30 limit the phenotype of transgenic mouse of the invention to include mouse that exhibit at least one or two diagnostic criteria for autism. Claims 31 and 32 limit the phenotype of transgenic mouse of claim 14 to include at least one or two diagnostic criteria for PDD-NOS. Because these claims embrace a different phenotype of transgenic knockout of the mouse exhibiting at least one diagnostic criteria for Asperger's syndrome, autism, PDD-NOS, the details of the disclosure provided by the applicant, in view of the prior art, must encompass a wide knowledge so that one of skilled in the art, at the time of invention by applicant, would be able to practice the invention as claimed by the applicant without undue burden being imposed on such Artisan. This burden has not been met because it would require undue experimentation to establish to produce a transgenic mouse comprising a homozygous disruption in endogenous (CIRL3-L) like gene, wherein the transgenic mouse exhibits at least one diagnostic criteria of a psychiatric disorder that is an anxiety related disorder selected from the list consisting of Asperger's syndrome, autism, PDD-NOS.

The specification teaches that instant invention relates to a methods for identifying molecules capable of modulating CIRL3-Like (CIRL3-L) protein, therapeutic uses for such identified molecules, and animal models of human psychiatric disorders and seizure-related disorders (see para. 2 of the specification). The specification discloses that CIRL3-L, which is a new GPCR protein (see paragraph 5). The disclosure defines "CIRL3-L" protein to sequence of SEQ ID NO: 1, or a functional equivalent thereof which has at least 90%, 95%, 99% homology in the nucleotide sequence encoding the protein or the amino acid sequence. It is noted that such a functional equivalent of CIRL3-L includes substitution, addition, deletion or insertion of at least one

nucleotide (see paragraph 33 of the specification). The invention embraces a knock-out wherein the CIRL3-L gene is altered or deleted such that the function of the endogenous CIRL3-L protein is reduced or ablated. The specification teaches CIRL-3L knockout mouse are socially impaired. It is noted that specification also discloses that the severity of the impairment depends upon the background strain of the mice (emphasis added) (see examples 3 and Figure 1). The knockout animal also showed gait abnormalities (example 3, figure2), impaired nociceptive responding on the hot plate test (see figure 3) and compulsive motor anxiety as evidenced by increased number of grooming bouts (see examples 3, and figure 4). The specification provides no evidence that a transgenic mouse carrying a homozygous disruption of CIRL3-L gene exhibit any specific phenotype that may be described as obsessive compulsive behavior or related disorders, screening for agents capable of reducing, ameliorating and/or inhibiting psychiatric disorders, motor activity, perseverative or compulsive behaviors as compared to a wild type mouse. The specification provides working examples and guidance relating to homozygous mice whose genome comprises disruption in CIRL-3L gene. The specification teaches a number of tests that were carried out on CIRL-3L disrupted mice without providing any guidance regarding the status of functional CIRL-3L protein made in the mice. It is not apparent from the specification what is considered as wild type control. Homozygous CIRL-3L mice are compared to wild type control for multiple behavioral analysis (Example 3). The data as presented does not disclose a coherent picture of the function of CIRL-3L gene or any condition associated with CIRL-3L knockout. The skilled artisan would have to perform undue experimentation to make and use the invention.

The art teaches the feasibility of creating a homozygous disruption of a targeted gene of interest and the creation of transgenic mouse containing the same. However, the art also teaches the resulting phenotype of a knockout mouse is exceedingly unpredictable. For example, Leonard (Immunological Reviews, 1995, 148: 98-114) discloses mice with disruption in the gc gene that was intended to be a model for X-linked severe combined immunodeficiency (XCIDS), but displays a variety of unexpected traits (Abstract). These knockout mice were expected to have thymocytes

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with decreased proliferation in response to stimulation with antibodies, but the thymocytes proliferated normally (pp 105, line 7). Griffiths (Microscopy Research and Technique 1998, 41: 344-358) taught that, despite a known role for the PLP gene based on spontaneous mutations in the gene, the knockout mouse failed to display any of the expected phenotype (pp 350, last paragraph). Furthermore, the state of the art suggests such unpredictability of phenotype is correlative to the genetic background of the knockout mouse. For example, Keri et al., (Proc Natl Acad Sci U S A. 2000; 97(1): 383-7) showed elevated levels of lutenizing hormone in transgenic can result in different reproductive system abnormalities including ovarian tumors. Schoonjans et al (Stem Cells, 2003; 21:90-97), for example state that the phenotype of gene-targeted mice is not only due to genetic alteration itself but also to the genetic background in which it is generated (pp93, discussion). Similarly, Wolfer et al (Trends in Neuroscience, 2002, 25 (7): 336-340) describe the unpredictability of phenotype resulting from gene disruption can be influenced by gene flanking the disrupted coding sequence and by the general genetic background of mouse strains, wherein congenic strains carrying the same null mutation can sometime show widely divergent phenotypes (pp 336, column 1-3). In the instant case, the F2 mice homozygous for the disrupted C1RL3-L gene have genotypes from two parents, due to the recombination events during gametogenesis (Gerali, Trends Neurosci. 1996, 19(5): 177-81, pp 178, lines 1-5). These mice are genotypically different from wild type littermates, and thus wild type littermates are not good controls for the null mice (Gerali, pp 178, col. 1, lines 6-18). This effect cause "linkage disequilibrium" between the transgenic and surrounding genes, producing a 'hitchhiking donor gene confound" (Lariviere et al J Pharmacol Exp Ther. 2001, 297(2): 467-73, pp 468, col. 1, para 3, lines 1-40) to overcome the "hitchhiking effect", two remedies are suggested: "testing a large number of mice" (Gerali pp 178, col. 2, lines 1-5) and many backcross (Lariviere, pp 468, col. 1, para. 3, lines 18-21). The specification describes data from F2 mice, except for the addition of social interaction data from the N2F2 generation, containing a higher B57B1/6 genetic background. It is noted that both generations shows social impairments, but the nature of the impairment shifted with the shift of background. Thus, in view of teaching of Gerali, it is apparent that any phenotypic

alteration observed in the presently claimed C1RL3-L transgenic knockout mice could be due to genetic background (Gerali, pp 179, col. 1, lines 9-14). There is no way to tell given the tests in the disclosure thus determining whether or not the phenotype of the mice seen due to distributed gene, "hitchhiking" alleles or compensation by C57/Bl gene cannot be determined from applicants data. These observations are further supported by the studies modeling experimental seizure disorder showing the importance of genetic background of mice that may influence the transgenic or knockout phenotype as unlinked gene can have a dramatic effect on the expected phenotype (Schauwecker et al, Progress in Brain Research, 2002, 135, 139-148). Schauwecker states "modifier gene can effect the expected phenotype" (see page 142, col. 2 para. 3). Thus, at the time of filing, it is evident from the art of record that the resulting phenotype of a knockout was considered unpredictable and it is not apparent whether or not the phenotype of the mice described in the instant application is due to disrupted gene, the hitchhiking alleles or compensation by other C57B gene. It is noted that applicant's amendments to claim 14 include transgenic mouse comprising deletion of C1RL-3L like gene exhibits at least one diagnostic criteria of Asperger's syndrome, autism, PDD-NOS. The knockout animal also showed gait abnormalities (example 3, figure2), impaired nociceptive responding on the hot plate test (see figure 3) and compulsive motor anxiety as evidenced by increased number of grooming bouts (see examples 3, and figure 4). However, specification also teaches that the severity of the impairment depends upon the background strain of the mice (emphasis added) (see examples 3 and Figure 1). Prior to instant invention, Rex et al (Pharmacol Biochem Behav. 1996; 54(1):107-11) indicated that genetic factors and breeding conditions substantially contribute to anxiety-motivated behaviors in animal models. These differences in anxiety-related behavior may also be related to biochemical differences. Rex et al also discuss the differences shown in anxiety-related behavior that might explain sometimes-contradictory effects following the treatment with anxiolytic or anxiogenic drugs. It is further noted that in a post filing art Tsuda et al (Behav Brain Res. 2006; 166(1): 19-31) also show the influence of genetic background of the mice on neurobehavioral traits (see abstract). It is noted that Tsuda et al show that acoustic startle responses were

increased in DBA/2 mice and decreased in C3H/He mice, but not altered in C57BL/6 or ddY mice. PPI levels were decreased in DBA/2 and C57BL/6 mice, but not in C3H/He or ddY mice. Locomotor activity was elevated only in DBA/2 mice. Similarly, Rodgers et al (Physiol Behav. 2002; 77(2-3):301-10) also discloses that three different inbred strains were less active as compared with the outbred Swiss-Webster strain in two exploration-based tests of anxiety-related behavior. Thus, it is apparent that transgenic mouse exhibiting one or two of the diagnostic criteria of Asperger's, autism or PDD-NOS would not be specific to the disorder, rather may be contributed by the genetic background or breeding conditions of the animal. The guidance provided by the specification amounts to invitation for the skilled Artisan to try and follow the disclosed instructions to make and use the claimed invention. The specification merely discloses a subset of phenotypes that fall within the broad scope of anxiety related disorder. Furthermore, mere capability to perform gene transfer in a mouse is not enabling because a desired phenotype cannot be predictably achieved by simply deletion of CIRL-3 L gene as recited in the claims. Holschneider et al. (Int J Devl Neuroscience, 2000, 18: 615-618) state that single genes are often essential in a number of different physiological processes. Hence, deletion of an individual gene may prove so drastic or so widespread as to create an amalgam of phenotypes whose interpretation becomes confounded by the interaction of various new physiologic changes (pp 615). Holschneider et al discuss various factors that contribute to the resulting phenotype of transgenic mice, including compensatory system that may be activated to mask the resulting phenotype; these compensatory changes may be due to differential expression of another gene, which may be regulated by the downstream product of the deleted gene. The function of CIRL3-L gene product is not completely known but has been speculated. Ichtchenko (J Biol Chem. 1999; 274(9): 5491-8) teaches that CIRL-1, CIRL-2, and CIRL-3 define a novel family of GPCRs wherein at least two of them, CIRL-1 and CIRL-2, are α -latrotoxin-binding proteins. Ichtchenko could not conclude any binding properties of CIRL-3 since he could not detect any α -latrotoxin binding of CIRL-3. However, art of record fail to establish this relationship and the specification lacks any teaching that establishes the function of CIRL3-L in the disclosed mice. In the instant case, claimed

invention recite a mouse showing at least one diagnostic criterion, which may not be related to CIRL-3L knockout given the unpredictability in the phenotype and influence of genetic background on phenotype an artisan for the specific reasons cited above it would have required undue experimentation for an artisan of skill to make and use the claimed invention.

In the instant case, the disclosure provided guidance in terms of expression level of CIRL-3L in brain but it does not detail provide any guidance in terms of its functional involvement in anxiety related disorder nor does it disclose a relationship to a condition associated with anxiety. Therefore, because an artisan does not know the function of CIRL-3L and does not know of any known relationship to a disease or condition, and artisan would not know how to use the transgenic knockout mouse. Furthermore, for an artisan to use or make the instant invention for its intended use, an artisan would have to determine the function of CIRL3-L and if there are any disease or specific conditions associated with CIRL-3L. Tecott et al (Am J Psychiatry 160:646-656, 2003) while reviewing the mouse behavioral models of psychiatric illnesses state "it is noteworthy that the assays of rodent depression- and anxiety-related behavior just discussed may be considered to model particular behavioral states rather than the full range of affective, cognitive, and neurovegetative symptoms characteristic of common psychiatric disorders. As discussed in other contributions to this issue, susceptibilities to these illnesses are polygenically determined, and the environmental contributions to their pathophysiology are incompletely understood. Therefore, current mouse models may be most productively used to examine the biological bases of individual features of psychiatric disorders rather than as comprehensive models of complex psychiatric syndromes (see page 653, col. 1, para. 2). An artisan would have to perform undue experimentation to first establish a link between the transgenic mouse with a specific condition and then test various symptoms seen the transgenic animal of the invention. It is emphasized that behavioral symptoms in disease or condition can be cause by a variety of mechanism that may or may not have any involvement of CIRL-3L gene (supra, genetic background of the mouse, compensatory mechanism or breeding condition). Given that the specification and art do not disclose a known disease causes

by impaired CIRL-3L, an artisan would not know if the instant mice represent a model for autism, PDD-NOS or Asperger's syndrome particularly given the unpredictability in achieving behavioral specific phenotype in mouse. An artisan would have to do further experimentation to determine if the symptoms associated with the knockout as associated and therefore representative a disease. In view of foregoing discussion, it is apparent that any difference of symptom seen in the instant transgenic

In view of the lack of teachings or guidance provided by the specification with regard to an enabled transgenic mouse comprising a deletion of CIRL3-L gene, the lack of teaching or guidance provided by the specifications to overcome the art recognized unpredictability of resulting phenotype and for the specific reasons cited above it would have required undue experimentation for an artisan of skill to make and use the claimed invention. It would require undue experimentation for an Artisan to make and use the claimed invention and/or working examples demonstrating the same, such invention as claimed by the applicant is not enabled for the claimed inventions.

Response to Arguments

Applicant's arguments filed May 9, 2007 have been fully considered but they are not fully persuasive. Applicants in their argument on page 8, paragraph 3-5 and on pages 9-11 state that amended claim 14 and new claims 27-32 are enabled by the specification. Applicants assert that no undue experimentation is required to practice the invention as presently claimed. Applicants argues that the phenotype of the claimed CIRL3-L transgenic mouse is apparent to a person of ordinary skill in the art in light of the specification, and that the specification does not fail to disclose a "coherent picture" of CIRL3-L function. Applicants assert that as amended claims now embrace a CIRL3-L knockout mouse wherein the mouse exhibits at least one diagnostic criterion of a psychiatric disorder that is an anxiety-related disorder selected from Asperger's syndrome, autism, and PDD-NOS. A person of ordinary skill, in light of the specification and knowledge in the art, would recognize that the disclosed phenotype of the CIRL3-L knockout mouse correlates well with diagnostic criteria set forth in the DSM-IV for the

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recited disorders. See, e.g., DSM-IV at 299.00 (diagnostic criteria for autistic disorder), 299.80 (diagnostic criteria for Asperger's disorder), and 299.80 (diagnostic criteria for PDD-NOS). The specification describes that the C1RL3-L knockout mouse displays one or more phenotypes that correlate with diagnostic criteria for one or more of the diagnostic criteria of the recited disorders, as reflected by, for example, the data of Figs. 1-5. Thus, no undue experimentation is required to arrive at a phenotype for the recited C1RL3-L knockout mouse. It is noted that applicants also provide the list of the DSM-IV diagnostic criteria for each disorder recited in the amended claims.

In response, Examiner would agree that as amended claims embrace a transgenic mouse exhibiting at least one diagnostic criterion that is an anxiety related disorder selected from Asperger's syndrome, autism and PDD-NOS. It is noted that specification teaches that the severity of the impairment depends upon the background strain of the mice (emphasis added) (see examples 3 and Figure 1). Although the knockout mouse of the invention showed gait abnormalities (example 3, figure2), impaired nociceptive responding on the hot plate test (see figure 3) and compulsive motor anxiety as evidenced by increased number of grooming bouts (see examples 3, and figure 4), however, specification fails to provide enabling support because examiner had previously indicated general unpredictability in attaining specific phenotype in a transgenic knockout comprising deletion of endogenous gene which is not associated or linked with any specific disease or condition. It is generally known in the art that genetic factors and breeding conditions substantially contribute to anxiety-motivated behaviors in animal models (Rex et al (Pharmacol Biochem Behav. 1996; 54(1):107-11). Rex discusses the differences shown in anxiety-related behavior that might explain sometimes-contradictory effects following the treatment with anxiolytic or anxiogenic drugs. It is further noted that in a post filing art Tsuda et al (Behav Brain Res. 2006; 166(1): 19-31) also showing the influence of genetic background of the mice on neurobehavioral traits (see abstract). It is noted that Tsuda et al show that acoustic startle responses were increased in DBA/2 mice and decreased in C3H/He mice, but not altered in C57BL/6 or ddY mice. Similarly, Rodgers et al (Physiol Behav. 2002;

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77(2-3):301-10) also discloses that three different inbred strains were less active as compared with the outbred Swiss-Webster strain in two exploration-based tests of anxiety-related behavior. Thus, it is apparent that pre and post filing art suggested strain, gender and breeding specific alteration in neurobehavioral traits. In the instant case, claims have been amended to include at least one diagnostic criterion of a psychiatric disorder that is a anxiety related disorder selected from Asperger's syndrome, autism and PDD-NOS. An artisan would have to carry out extensive experimentation to make and use the invention, and such experimentation would have been undue because an artisan does not know the function of CIRL-3L and does not know of any known relationship to a disease or condition, and therefore artisan would not know how to use the transgenic knockout mouse. Furthermore, claimed invention recite a mouse showing at least one diagnostic criterion, which may or may not be related to CIRL-3L knockout given the unpredictability in the phenotype and influence of genetic background on phenotype an artisan for the specific reasons cited above it would have required undue experimentation for an artisan of skill to make and use the claimed invention.

Withdrawn-Claim Rejections - 35 USC § 112

Claim 14 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of amendment to claims 14 and cancellation of claims 15-26.

Conclusion

No Claims allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anoop Singh whose telephone number is (571) 272-3306. The examiner can normally be reached on 9:00AM-5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272- 4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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